Crompton

Product Safety and Regulatory Affairs

201-14968

December 22, 2003

Marianne L. Horinko
Acting Administrator
U.S. Environmental Protection Agency
P.O. Box 1473
Merrifield, VA 22116

Attn: Chemical Right To-Know Program

Dear Administrator Horinko,

Crompton Corporation is submitting the enclosed Robust Summary and Test Plan for the following chemical:

2,4,8,10-Tetraoxa-3,9-diphosphaspiro[5.5]undecane, 3,9-bis[2,4-bis(1,1-dimethylethyl)phenoxy]- (CAS RN 26741-53-7)

If you have any questions, please contact me at 203-573-3390 or e-mail to mark_Thomson@cromptoncorp.com

Sincerely,

Dr. Mark A. Thomson
Manager, Toxicology & International Product Registration
Crompton Corporation
Middlebury, CT 06749
USA

Responsible Care®
A Public Commitment

201-14968

HIGH PRODUCTION VOLUME (HPV)
CHEMICAL CHALLENGE PROGRAM

TEST PLAN

For

3,9-bis(2,4-di-tert-butylphenoxy)-2,4,8,10-tetraoxa-3,9-diphosphaspiro[5.5]undecane

CAS No. 26741-53-7

Submitted to the US EPA

BY

Crompton Corporation.

Table of Contents

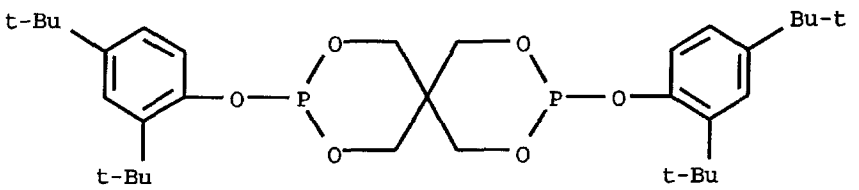
Test Plan for Dinoseb

1. General Information

1.1 CAS Number: 26741-53-7

1.2 Molecular Weight: 604.71

1.3 Structure and formula: $C_{33}H_{50}O_6P_2$



1.4 Introduction

3,9-bis(2,4-di-tert-butylphenoxy)-2,4,8,10-tetraoxa-3,9-diphosphaspiro[5.5]undecane (Ultranox 626) is used as an antioxidant for polyolefins, polyesters, styrenics, engineering thermoplastics, PVC, elastomers and adhesives. The use of Ultranox 626 is sanctioned by the FDA for food contact applications under 21CFR178.2010 covering antioxidants and/or stabilizers for polymers.

2. Review of Existing Data and Development of Test Plan

Crompton Corporation has undertaken a comprehensive evaluation of all relevant data on the SIDS endpoints of concern for DNBP.

The availability of the data on the specific SIDS endpoints is summarized in Table 1. Table 1 also shows data gaps that will be filled by additional testing.

Table 1: Available adequate data and proposed testing on Ultranox 626

CAS No. 10081-67-1	Information Available?	GLP	OECD Study?	Other Study?	Estimation Method?	Acceptable?	SIDS Testing required?
	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
Physicochemical							
Melting Point	Y	Y	Y			Y	N
Boiling Point	Y	Y	Y			Y	N
Vapour Pressure	Y				Y	Y	N
Water Solubility	Y				Y	Y	N
Partition Coefficient (Kow)	Y				Y	Y	N
Environmental Fate							
Biodegradation	Y				Y	Y	N
Hydrolysis	Y						Y
Photodegradation	Y				Y	Y	N
Transport and Distribution between Environmental Compartments	Y				Y	Y	N
Ecotoxicology							
Acute Fish	Y				Y	Y	N
Acute Daphnia	Y				Y	Y	N
Acute Algae	Y				Y	Y	N
Toxicology							
Acute Oral	Y	N	N			Y	N
Repeat Dose toxicity	Y	N	N			Y	N
Genetic toxicity – Gene mutation	Y	N				Y	N
Genetic toxicity – Chromosome aberration	Y	Y	Y			Y	N
Reproductive toxicity	N						N
Developmental toxicity/teratogenicity	Y	N	N			Y	N

A. Evaluation of Existing Physicochemical Data and Proposed Testing

1. Melting Point

The melting point was found to be between 173 – 180°C in a guideline study conducted to GLP.

2. Boiling Point

The boiling point was found to be greater than 311°C in a guideline study conducted to GLP

3. Vapor Pressure

The vapor pressure was estimated to be 2.9×10^{-12} hPa at 25°C using MPBPWIN v 1.40.

4. Water Solubility

The water solubility is estimated to be 5.67×10^{-8} mg/L at 25°C using WSKOW v 1.40.

5. Partition Coefficient

The Log Pow is estimated to be 10.9 using KOWWIN v 1.66.

Summary of Physicochemical Properties Testing: Existing data for melting point, boiling point, vapour pressure, partition coefficient and water solubility are considered to fill these endpoints adequately.

B. Evaluation of Existing Environmental Fate Data and Proposed Testing

1. Biodegradation

The biodegradability of the chemical has been estimated using Biowin v4.00 and the results indicate the chemical to not be readily biodegradable. The chemical contains no biodegradable groups, therefore no biodegradation testing is proposed.

2. Hydrolysis

A study to fill this endpoint will be performed.

3. Photodegradation

The potential for photodegradation of DNBP has been estimated using the AOPWIN v1.90, and indicated atmospheric oxidation via OH radicals reaction with a half-life of 1.166 hours.

4. Transport and Distribution between Environmental Compartments

An Epiwin Level III Fugacity Model calculation has been conducted DNBP and indicates distribution mainly to sediment and, to a lesser extent, soil for emissions of 1000 kg/hr simultaneously to air water and soil compartments.

Summary of Environmental Fate Testing: Existing data for photodegradation, biodegradation and transport and distribution between environmental compartments are considered to fill these endpoints adequately. A hydrolysis study (OECD 111) will be conducted.

C. Evaluation of Existing Ecotoxicity Data and Proposed Testing

1. Acute Toxicity to Fish

The LC_{50} (96 h) was estimated to be 1.93×10^{-6} mg/L using ECOSAR v 0.99g. This is greater than the estimated limit of solubility of the substance.

2. Acute Toxicity to Daphnia

The EC_{50} (48 h) was estimated to be $3.82x10^{-6}$ mg/L using ECOSAR v 0.99g. This is greater than the estimated limit of solubility of the substance.

3. Acute Toxicity to Algae

The EC_{50} (96 h) was estimated to be 3.99x10-6 mg/L using ECOSAR v 0.99g. This is greater than the estimated limit of solubility of the substance.

Summary of Ecotoxicity Testing: Ultranox 626 is estimated to be toxic to the environment only at levels above its limit of solubility. No further testing is proposed.

D. Evaluation of Existing Human Health Effects Data and Proposed Testing

1. Acute Oral Toxicity

The acute oral toxicity of Ultranox 626 is reported as LD_{50} = 5580 mg/kg in a rat study. In a study conducted using Leghorn hens, an LD_{50} of >6080 mg/kg was reported.

2. Acute Inhalation Toxicity (non-SIDS endpoint)

An LC_{50} of >2000 mg/m^3 was reported in rats after a 1-hour exposure to Ultranox 626.

3. Acute Dermal Toxicity (non-SIDS endpoint)

Acute dermal toxicity was reported as LD_{50} > 2000 mg/kg using rabbits in an OECD 402 study conducted to GLP.

4. Acute I.P. Toxicity (non-SIDS endpoint)

An LD_{50} (mouse) of 14.1 – 20.2 mg/kg is reported in the literature.

5. Skin Irritation (non-SIDS endpoint)

Ultranox 626 was found to be corrosive to rabbit skin in a study conducted to 16CFR 1500.42.

6. Sensitization (non-SIDS endpoint)

The substance was not sensitizing (0/10 sensitization rate) to guinea pigs in a study conducted to OECD 406 under GLP.

7. Repeat Dose Toxicity

In a 90-day oral feed study conducted using rats, the observed NOAEL was 300 ppm. Microscopic lesions seen in the livers and spleens of female rats in the 1000 ppm group were considered to be substance related.

In a 4-month oral dose study conducted using dogs a NOAEL of 12 mg/kg b.w. was reported. Seven out of 8 dogs dosed at 40 mg/kg b.w. displayed degenerative myelin lesions, which were considered to be dose-related.

In a 2-year oral feed study using rats, a NOAEL of 500 ppm (highest dose tested) was reported. No effects were seen at any of the dose levels used.

8. Genotoxicity

Ultranox 626 tested negative in an Ames test using *Salmonella typhimurium* strains TA97, TA98, TA100 and TA102 and *Escherichia coli* strain WP2 (PKM101) with and without metabolic activation.

In a chromosome aberration test (OECD 473) the substance tested positive without metabolic activation using Arochlor 1254-induced rat liver S9.

In an in vivo mouse micronucleus assay (OECD 474) no genotoxic effects were observed.

9. Reproductive and Developmental Toxicity

Female rabbits were dosed orally at up to 200 mg/kg b.w./day with the substance on days 16-18 of gestation and the fetuses removed for examination on day 29 of gestation. No maternal effects were noted in any dose group. 3/15 rabbits miscarried in the high dose group, however the study authors considered this result to be only bordering significance. The number of implantations and the number and weight of the fetuses were not significantly different from the control values. There was no difference in the distribution between male and female fetuses and there were not significant numbers of malformations observed.

Reproductive organs were examined in the 2-year oral feed study in rats described in section 7 above. No greater frequency of anomalies was observed in treated rats compared to controls. In the interests of animal welfare, it is considered to be unnecessary to conduct a separate reproductive toxicity study based on the evidence available from the developmental toxicity study and the 2-year repeat dose study.

Summary of Human Health Effects Testing: All endpoints are considered to have been filled adequately.

3. Evaluation of Data for Quality and Acceptability

The collected data were reviewed for quality and acceptability following the general US EPA guidance [2] and the systematic approach described by Klimisch et al [3]. These methods include consideration of the reliability, relevance and adequacy of the data in evaluating their usefulness for hazard assessment purposes. This scoring system was only applied to ecotoxicology and human health endpoint studies per EPA recommendation [4]. The codification described by Klimisch specifies four categories of reliability for describing data adequacy. These are:

(1) Reliable without restriction: Includes studies or data complying with Good Laboratory Practice (GLP) procedures, or with valid and/or internationally accepted testing guidelines, or in which the test parameters are documented and comparable to these guidelines.

(2) Reliable with Restrictions: Includes studies or data in which test parameters are documented but vary slightly from testing guidelines.

(3) Not Reliable: Includes studies or data in which there are interferences, or that use non-relevant organisms or exposure routes, or which were carried out using unacceptable methods, or where documentation is insufficient.

(4) Not Assignable: Includes studies or data in which insufficient detail is reported to assign a rating, e.g. listed in abstracts or secondary literature.

4. References

[1] US EPA, EPI Suite Software, 2000

[2] USEPA (1998). Guidance for Meeting the SIDS Requirements (The SIDS Guide). Guidance for the HPV Challenge Program. Dated 11/2/98.

[3] Klimisch, H.-J., et al (1997). A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data. Regul. Toxicol. Pharmacol. 25:1-5

[4] USEPA (1999). Determining the Adequacy of Existing Data. Guidance for the HPV Challenge Program. Draft dated 2/10/99.

1. General Information

Id 26741-53-7
Date 12.12.2003

201-14968

IUCLID

Data Set

Existing Chemical	:	ID: 26741-53-7
CAS No.	:	26741-53-7
EINECS Name	:	3,9-bis(2,4-di-tert-butylphenoxy)-2,4,8,10-tetraoxa-3,9-diphosphaspiro[5.5]undecane
EC No.	:	247-952-5
Molecular Formula	:	C33H50O6P2

Status	:	
Memo	:	US HPV ULTRANOX 626 Crompton Corp
Printing date	:	12.12.2003
Revision date	:	
Date of last update	:	12.12.2003
Number of pages	:	1
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

2.1 MELTING POINT

Value	:	173 - 180 °C
Sublimation	:	
Method	:	OECD Guide-line 102 "Melting Point/Melting Range"
Year	:	2003
GLP	:	yes
Test substance	:	Chemical name: 2,4,8,10-tetraoxa-3,9-diphosphaspiro [5.5]undecane, 3,9-bis[2,4-bis(1,1-dimethylethyl)phenoxy]- CAS No.: 26741-53-7 Product Name: U626 Lot No.: H42265
Result	:	No color change was observed during melting point determinations, which was consistent with U626 being chemically stable at the melting point.
Reliability	:	(1) valid without restriction
12.12.2003		(14)

2.2 BOILING POINT

Value	:	> 311 °C at 1015 hPa
Decomposition	:	no
Method	:	OECD Guide-line 103 "Boiling Point/boiling Range"
Year	:	2003
GLP	:	yes
Test substance	:	Chemical name: 2,4,8,10-tetraoxa-3,9-diphosphaspiro [5.5]undecane, 3,9-bis[2,4-bis(1,1-dimethylethyl)phenoxy]- CAS No.: 26741-53-7 Trade name: U626 Lot No. H42265
Remark	:	Estimation using MPBPWIN v 1.40 (US EPA., EPIWIN v 3.10, EPI Suite Software, 2000) gives a boiling point of 595°C
Result	:	The duplicate U626 warming curves did not show a distinct boiling plateau up to the maximum temperature of 312°C (at 101.5 kPa). This was supported by the fact that U626 was not observed to boil during the test. No U626 color change nor smoke was observed during the test.
Reliability	:	(1) valid without restriction
12.12.2003		(13)

2.4 VAPOUR PRESSURE

Value	:	.0000000000029 hPa at 25 °C
Decomposition	:	
Method	:	other (calculated): MPBPWIN v 1.40
Year	:	2003
GLP	:	
Test substance	:	Chemical name: 2,4,8,10-tetraoxa-3,9-diphosphaspiro [5.5]undecane, 3,9-bis[2,4-bis(1,1-dimethylethyl)phenoxy]- CAS No.: 26741-53-7
Test condition	:	Melting point = 173°C (experimental) Boiling Point = 595 (estimated)
Reliability	:	(2) valid with restrictions
12.12.2003		(16)

2.5 PARTITION COEFFICIENT

Partition coefficient	:	octanol-water
Log pow	:	10.9 at °C
pH value	:	
Method	:	other (calculated): KOWWIN v 1.66
Year	:	2003
GLP	:	
Test substance	:	Chemical name: 2,4,8,10-tetraoxa-3,9-diphosphaspiro [5.5]undecane, 3,9-bis[2,4-bis(1,1-dimethylethyl)phenoxy]- CAS No.: 26741-53-7
Reliability	:	(2) valid with restrictions

12.12.2003

(16)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in	:	Water
Value	:	at °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	other: calculated using WSKOW v 1.40
Year	:	2003
GLP	:	
Test substance	:	Chemical name: 2,4,8,10-tetraoxa-3,9-diphosphaspiro [5.5]undecane, 3,9-bis[2,4-bis(1,1-dimethylethyl)phenoxy]- CAS No.: 26741-53-7
Remark	:	An OECD 105 study is currently underway to fill this endpoint.
Result	:	Water solubility = 5.67E-8 mg/L
Test condition	:	Melting point = 173°C (experimental) Log Kow = 10.9 (estimated)
Reliability	:	(2) valid with restrictions

12.12.2003

(16)

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	1500000 molecule/cm³
Rate constant	:	.000000000000011 cm³/(molecule*sec)
Degradation	:	% after
Deg. product	:	
Method	:	other (calculated): estimation using AOPWIN v1.90
Year	:	2003
GLP	:	
Test substance	:	Chemical name: 2,4,8,10-tetraoxa-3,9-diphosphaspiro [5.5]undecane, 3,9-bis[2,4-bis(1,1-dimethylethyl)phenoxy]- CAS No.: 26741-53-7
Result	:	T1/2 = 1.166 hours
Reliability	:	(2) valid with restrictions

08.12.2003 (16)

3.1.2 STABILITY IN WATER

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	:	fugacity model level III
Media	:	
Air	:	% (Fugacity Model Level I)
Water	:	% (Fugacity Model Level I)
Soil	:	% (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Method	:	other: EPIWIN Level III Fugacity Model
Year	:	2003
Test Substance	:	Chemical name: 2,4,8,10-tetraoxa-3,9-diphosphaspiro [5.5]undecane, 3,9-bis[2,4-bis(1,1-dimethylethyl)phenoxy]- CAS No.: 26741-53-7
Test condition	:	Henry's Law Constant: 3.24E-9 atm-m3/mol (Henrywin) Vapor pressure: 2.9E-12 mmHg (Mpbpwin) Melting Point: 173°C (experimental) Log Kow: 10.9 (Kowwin) Soil Koc: 3.26E10 (calc by model)

	Mass Amount (percent)	Half-life (hr)	Emissions (kg/hr)
Air	0.0175	2.33	1000
Water	1.25	3600	1000
Soil	33.1	3600	1000
Sediment	65.6	14400	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)

Water	1.07E-19	40.8	212	1.36	7.06
Soil	2.14E-21	1080	0	36	0
Sediment	1.9E-19	535	222	17.8	7.41

Persistence time: 5640 hr
Reaction time: 6680 hr
Advection time: 36500 hr
Percent reacted: 84.5
Percent advected: 15.5

Half-lives (hr), (based upon Biowin (ultimate) and Aopwin):
Air: 2.33
Water: 3600
Soil: 3600
Sediment: 14400
Biowin estimate: 0.802

Advection times (hr):
Air: 100
Water: 1000
Sediment: 5E+4

Reliability : (2) valid with restrictions
08.12.2003

(16)

3.5 BIODEGRADATION

Type : aerobic
Inoculum :
Deg. product :
Method : other: Estimation using BIOWIN v4.00
Year : 2003
GLP :
Test substance : Chemical name: 2,4,8,10-tetraoxa-3,9-diphosphaspiro [5.5]undecane, 3,9-bis[2,4-bis(1,1-dimethylethyl)phenoxy]-
CAS No.: 26741-53-7

Result : MITI Linear Biodegradation Probability: -0.6156
MITI Non-linear Biodegradation Probability: 0.000

The substance is predicted to be not readily biodegradable

Reliability : (2) valid with restrictions
12.12.2003

(16)

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	other: estimation
Species	:	
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	1.93E-6
Method	:	other: calculated using ECOSAR v 0.99g
Year	:	2003
GLP	:	
Test substance	:	Chemical name: 2,4,8,10-tetraoxa-3,9-diphosphaspiro [5.5]undecane, 3,9-bis[2,4-bis(1,1-dimethylethyl)phenoxy]- CAS No.: 26741-53-7
Reliability	:	(2) valid with restrictions

12.12.2003 (16)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	other: estimation
Species	:	Daphnia sp. (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
EC50	:	3.82E-6
Method	:	other: calculated using ECOSAR v 0.99g
Year	:	2003
GLP	:	
Test substance	:	Chemical name: 2,4,8,10-tetraoxa-3,9-diphosphaspiro [5.5]undecane, 3,9-bis[2,4-bis(1,1-dimethylethyl)phenoxy]- CAS No.: 26741-53-7
Reliability	:	(2) valid with restrictions

12.12.2003 (16)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	
Endpoint	:	
Exposure period	:	96 hour(s)
Unit	:	mg/l
EC50	:	3.99E-6
Method	:	other: calculated using ECOSAR v 0.99g
Year	:	2003
GLP	:	
Test substance	:	Chemical name: 2,4,8,10-tetraoxa-3,9-diphosphaspiro [5.5]undecane, 3,9-bis[2,4-bis(1,1-dimethylethyl)phenoxy]- CAS No.: 26741-53-7
Reliability	:	(2) valid with restrictions

12.12.2003 (16)

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	5580 mg/kg bw
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	100
Vehicle	:	
Doses	:	1300 - 15300 mg/kg
Method	:	other:IBTL method
Year	:	1975
GLP	:	no
Test substance	:	Chemical name: 2,4,8,10-tetraoxa-3,9-diphosphaspiro [5.5]undecane, 3,9-bis[2,4-bis(1,1-dimethylethyl)phenoxy]- CAS No.: 26741-53-7 Product Name: Ultranox 626 (Weston 6140)
Reliability	:	(4) not assignable

12.12.2003 (4)

Type	:	LD50
Value	:	> 6080 mg/kg bw
Species	:	hen
Strain	:	Leghorn
Sex	:	female
Number of animals	:	24
Vehicle	:	other: corn oil
Doses	:	800, 1200, 1800, 2700, 4050, 6080 mg/kg bw
Method	:	other: Biodynamics Inc method
Year	:	1980
GLP	:	no
Test substance	:	Chemical name: 2,4,8,10-tetraoxa-3,9-diphosphaspiro [5.5]undecane, 3,9-bis[2,4-bis(1,1-dimethylethyl)phenoxy]- CAS No.: 26741-53-7 Trade name: Weston 1452 Purity: 99.5% Lot No.: PP-357
Method	:	No of animals/sex/dose: 4 hens/dose Vehicle: Corn oil Route of administration: Gavage
Result	:	Number of deaths at each dose level: No hens died during the study Clinical signs: Occasional hens showed green or yellow discoloration of the feces on the day of dosing. This reflects the use of corn oil vehicle and is not considered to indicate a response to treatment. There were no signs of toxicity and the hens remained normal in respect of appearance, mood, locomotor function and body weight throughout the observation period. Necropsy findings: Occasional findings of liver discoloration . This is a common pathological entity in hens of this age and is not considered to reflect any delayed or residual response to treatment.
Test condition	:	Age: 12 months Weight: 1.3 - 1.9 kg Volume administered: 10 mL/kg Post dose observation period: 14 days
Reliability	:	(2) valid with restrictions

08.12.2003 (1)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	LC50
Value	:	> 2000 mg/m³
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	10
Vehicle	:	
Doses	:	2 mg/L
Exposure time	:	1 hour(s)
Test Substance	:	Chemical name: 2,4,8,10-tetraoxa-3,9-diphosphaspiro [5.5]undecane, 3,9-bis[2,4-bis(1,1-dimethylethyl)phenoxy]- CAS No.: 26741-53-7 Trade name: weston 61440
Result	:	None of the animals died and all the animals appeared normal during the 14 day oservation period. The gross pathological autopsy of all 10 animals showed normal appearance of the organs of the thorax and the abdomen.
Reliability	:	(4) not assignable

12.12.2003 (11)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Value	:	> 2000 mg/kg bw
Species	:	rabbit
Strain	:	New Zealand white
Sex	:	male/female
Number of animals	:	10
Vehicle	:	
Doses	:	2000 mg/kg bw
Method	:	OECD Guide-line 402 "Acute Dermal Toxicity"
Year	:	1994
GLP	:	yes
Test substance	:	Chemical name: 2,4,8,10-tetraoxa-3,9-diphosphaspiro [5.5]undecane, 3,9-bis[2,4-bis(1,1-dimethylethyl)phenoxy]- CAS No.: 26741-53-7 Trade name: Ultranox 626 Lot No.: HCC033
Result	:	Mortality: There were no deaths during the study

Clinical observations: 5 rabbits had abnormal defecation (soft stool, mucoid feces) on day 0 or 1. One of these animals also had wet, and subsequently, dry brown urogenital matting. These findings were considered to be a result of the bandage/restraint procedures used and not related to the test material. An additional spontaneaous occurrence of soft stool was noted on day 9 for one animal. There were no other findings.

Dermal observations: The test material induced generally very slight to slight erythema on all rabbits and very slight to slight edema on 8 rabbits. There was a single occurrence of moderate erythema at the day 1 observation. Desquamation was present on five sites by day 7. There were no other dermal findings. One site had very slight erythema at study termination (day 14).

Body weights: There wer no remarkable changes or differences noted in body weights during the study.

Necropsy: Accessory splenic tissue, a common congenital abnormality in this strain of rabbit, was noted for four animals at the terminal necropsy. There were no other gross necropsy findings for all examined tissues.

Test condition : Age: Approximately 11 weeks old
Weight: 2014 - 2224 g at study initiation
Post dose observation period: 14 days

Reliability : (1) valid without restriction
Guideline study conducted to GLP

28.11.2003 (10)

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	.5 g
Exposure	:	Occlusive
Exposure time	:	24 hour(s)
Number of animals	:	6
Vehicle	:	physiol. saline
PDII	:	
Result	:	corrosive
Classification	:	
Method	:	other: 16CFR 1500.42
Year	:	1981
GLP	:	no
Test substance	:	Chemical name: 2,4,8,10-tetraoxa-3,9-diphosphaspiro [5.5]undecane, 3,9-bis[2,4-bis(1,1-dimethylethyl)phenoxy]- CAS No.: 26741-53-7 Trade name: Weston XP-1532 Lot No.: 1198
Result	:	Necrotic skin occurred in all animals at 24 and 72 hours. The responses for abraded and intact skin were the same.
Reliability	:	(2) valid with restrictions

12.12.2003 (3)

5.3 SENSITIZATION

Type	:	other: Footpad method
Species	:	guinea pig
Concentration	:	1st: Induction 1 % other: injected into footpad 2nd: Challenge 10 % open epicutaneous 3rd:
Number of animals	:	20
Vehicle	:	other:Induction: Freund's adjuvant, Challenge: acetone/dioxane/guinea pig fat 7:2:1
Result	:	not sensitizing
Classification	:	not sensitizing
Method	:	OECD Guide-line 406 "Skin Sensitization"
Year	:	1992
GLP	:	yes
Test substance	:	Chemical name: 2,4,8,10-tetraoxa-3,9-diphosphaspiro [5.5]undecane, 3,9-bis[2,4-bis(1,1-dimethylethyl)phenoxy]- CAS No.: 26741-53-7 Trade name: Ultranox 626 Lot No.: U626-1
Result	:	Primary irritation screen: No signs of erythema or edema were evident for the animals that were administered 1, 3 or 10% of the test material.

Sensitization study: No signs of erythema or edema were noted at the 24 or 48 hour for animals previously induced with either Freund's adjuvant (control animals) or with 1% of the test material in Freund's adjuvant).

No toxic effects or systemic clinical signs were ntoed during the study.

All animals gained weight normally during the study.

Test condition : Strain: Crl:(HA)BR VAF/PlusT

Primary irritation screen:

No. of animals: 5/dose
Doses: 1.0%, 3.0%, 10.0%
Sex: Not determined
Body weight range: 571 - 741 g
Age: Not determined

Sensitization study:
No. of animals: 20; 10 control, 10 test
Sex: Female
Body weight range: 361 - 442 g
Age at study initiation: 6 - 7 weeks

Reliability : (1) valid without restriction
Guideline study conducted to GLP

28.11.2003 (15)

5.4 REPEATED DOSE TOXICITY

Type	:	
Species	:	rat
Sex	:	male/female
Strain	:	other: Charles River CD
Route of admin.	:	oral feed
Exposure period	:	90 days
Frequency of treatm.	:	daily
Post exposure period	:	none
Doses	:	0, 100, 300, 1000 ppm
Control group	:	yes, concurrent vehicle
NOAEL	:	300 ppm
Method	:	other: IRDC method
Year	:	1979
GLP	:	no
Test substance	:	Chemical name: 2,4,8,10-tetraoxa-3,9-diphosphaspiro [5.5]undecane, 3,9-bis[2,4-bis(1,1-dimethylethyl)phenoxy]- CAS No.: 26741-53-7 Trade name: Weston XR-1532 Lot No.: 225-35 Impurities: 1% tris-isopropanolamine
Result	:	Body weight: The group mean body weights of both the low and mid dose male and female rats were greater than control values, and both groups of high dose males and females had group mean body weights lower than controls. Food/water consumption: Low and mid dose male rats consumed slightly more food than did controls, while high dose males ate slightly less than control. All of the groups of females consumed approximately equivalent amounts of food. Clinical signs: No signs of overt toxicity were observed aming the treated

included hair loss. missing or malaligned upper incisor, excessive lacrimation, red material around the eyes, leaning to left, red or swollen eyes, rales, corneal opacity, swollen ventral neck, swollen conjunctiva and dilated pupil.

Ophthalmologic findings: There were no compound related effects noted during the 3-month ophthalmic examinations.

Hematology: No compound related effects on the results of the hematologic tests were observed.

Clinical biochemistry: No compound related effects on the results of the biochemical tests were observed.

Mortality: No compound related effects on survival rates were noted (one female rat in the 1000 ppm group died during the study).

Gross pathology: No compound related gross lesions were observed in any of the rats from the treated groups. No tumors were noted upon gross examination.

Organ weight changes: Statistically significant variations ($p<0.01$) in absolute weights of kidneys of amle rats at 300 ppm and hearts of male rats at 100 and 300 ppm were not considered compound related.

Histopathology: Microscopic lesions considered probably compound related were seen in livers and spleens of the female rats from the 1000 ppm group. This consisted of very slight to slight extramedullary hematopoiesis in these organs. This lesion was not present in rats from the control and the 300 ppm groups but was seen in one rat from the 100 ppm group. Other microscopic lesions in livers and those seen in other organs in the control and 1000 ppm groups were considered spontaneous in nature and unrelated to the administration of the compound.

Test condition : Statistical methods: All statistical analyses compared the treatment groups with the control group by sex. Body weights, food consumption, absolute and relative organ weights and hematology, biochemistry and urinalysis parameters were compared by analysis of variance (one-way), Bartlett's test for homogeneity of variances and the appropriate t-test (for equal or unequal variances) as described by Steel and Torrie using Dunnett's multiple comparison tables to judge significance of differences.

Test subjects:

Weight at study initiation: 80-107g (male), 77-98g (female)

No. of animals/sex/dose: 20 male, 20 female

Study Design:

Vehicle: Feed (Rodent Laboratory Chow)

Clinical observations performed and frequency: The rats were observed twice daily for signs of overt toxicity and mortality. Detailed observations were recorded weekly and included the size, incidence and location of all palpable masses. Individual body weights were recorded weekly and individual food consumption was recorded daily.

Organs examined at necropsy: The following tissues from 10 males and 10 females from the control group and the 1000 ppm group were examined

pancreas, urinary bladder, bone marrow (sternum), prostate/uterus, seminal vesicles, testes/ovaries, brain, heart, lung and bronchi, sciatic nerve, pituitary, thyroid and parathyroid, mesenteric lymph node, mandibular lymph node, spinal cord, salivary gland (submaxillary), skeletal muscle (thigh), skin, mammary gland, thymus, kidneys, any other tissue with gross lesions.

Bone marrow smears from all rats were made at necropsy and examined microscopically.

Additionally, livers and spleens from 10 male and 10 female rats from the 100 ppm and 300 ppm groups were examined.

Reliability : (2) valid with restrictions
Well conducted study, prior to GLP

05.12.2003 (9)

Type	:	
Species	:	dog
Sex	:	male/female
Strain	:	Beagle
Route of admin.	:	other: oral via gelatin capsule
Exposure period	:	4 months
Frequency of treatm.	:	daily
Post exposure period	:	
Doses	:	0, 4, 12, 40 mg/kg/day
Control group	:	yes
NOAEL	:	12 mg/kg bw
Method	:	other: Bio/dynamics Inc method
Year	:	1980
GLP	:	no
Test substance	:	Chemical name: 2,4,8,10-tetraoxa-3,9-diphosphaspiro [5.5]undecane, 3,9-bis[2,4-bis(1,1-dimethylethyl)phenoxy]- CAS No.: 26741-53-7 Trade name: Weston XR-1532 Lot No.: 1532-003-04189-X Purity: 100%

Result : Mortality: One high dose female was sacrificed in a moribund condition after 86 days on test. All of the remaining control and treated animals survived the duration of the study.

Physical and neurological observations: The only physical and neurological observations noted during the study which were considered related to the administration of the test substance involved the high dose female which was sacrificed in a moribund condition. On test day 51, this animal exhibited the first signs of uncoordination of the hind limbs and a poor righting reflex. These symptoms progressed and by test day 58, the animal displayed a lack of coordination of both the fore and hind limbs. The animal became progressively recumbent as the uncoordination progressed to rigid fore and hind limb paralysis. During this time the animal was offered canned dog food in an attempt to increase its food consumption and maintain its body weight. However this was unsuccessful and the animal was sacrificed in a moribund condition on test day 86.

Ophthalmology: There were no ocular abnormalities observed after 3 or 4 months of study which could be attributed to the test substance.

Body weight and food consumption: The mean body weights of all treated males were slightly greater than control prior to initiation of dosing (4-5%) and throughout the 4 month treatment period. At 18 weeks these differences from control were 25%, 20%, and 21% in the low, mid and high

lower in the low (13%), mid (12%) and high (17%) dose males when compared to the control values over the 18 week period of test substance administration. Mean body weight and food consumption values for the control and treated females were unremarkable throughout the study with the exception of one high dose female. During week 9 this animal began to exhibit decreases in food consumption and body weight. These decreases continued over the next 3 weeks and the animal was sacrificed in a moribund condition on test day 86.

Hematology and clinical chemistry: At 1 month the mean platelet counts of the treated males were significantly lower than control. However, these differences were attributed to a slightly greater mean platelet counts in the control group rather than an effect of the test substance. Other differences from control were noted in some of the hematology and clinical chemistry parameters evaluated. However, these differences were not dose related or consistent over time and therefore were not considered related to administration of the test material.

Urinalysis: The urinalysis data collected after 1, 3 and 4 months of study were unremarkable and revealed no differences between control and treated groups which could be attributed to the administration of the test substance.

Organ weights and organ/body weight ratios: Slight diferences from control, some statistically significant, were observed in the mean absolute and relative organ weights of the treated animals. These variations were attributed to differences in terminal body weights and normal biological variation between animals. There were no differences observed in absolute or relatve organ weights which were attributed to the administration of the test substance.

Pathology: A subacute, eosinophilic pneumonia was observed microscopically in four of eight high dose animals, one of eight mid dose animals and two of eight low dose animals. This condition was not observed in any of the control animals. The etiology of the pulmonary lesions could not be determined. Seven of the eight high dose animals displayed degenerative myelin lesions. These lesions were confined to the high dose group and were considered related to the administration of the test material. One animal (the female which died) displayed clinical manifestations of several abnormalities of the axonal fibers and myelin.

Test condition : Statistical methods: Hematology and clinical chemistry: Test substance groups were compared to control by the F-test and Student's T-test. When variances differed significantly (F-test), Student's t-test was appropratiately modified using Cochrane's approximation (t'). Snedecor, G.W. & Cochran, W.G. (1967) Statistical Methods, 6th ed. Iowa State University Press, Ames, pp 104-106, 114-119. Body weight, Food consumption, Organ weights and organ/body weight ratios: Treated groups were ocmpared to control. Dunnett, C.W. (1964) J. Am. Stat. Assn. 50, 1096-1121 and Biometrics 20, 482 (1964).

Test subjects:

Weight at study initiation: 80-107g (male), 77-98g (female)

No. of animals/sex/dose: 4/sex/dose

Study Design:

Vehicle: None

Clinical observations performed and frequency: Twice daily for mortality

Detailed physical examination: Pretest and weekly thereafter

Neurologic examination: Pretest and monthly thereafter

Ophthalmoscopic examination: Pretest, 3 and 4 months

Body weight: Pretest, weekly during treatment and terminally

Food consumption: Pretest and weekly thereafter

Laboratory studies: Pretest and monthly thereafter. Parameters evaluated - Hematology: hemoglobin, hematocrit, erythrocytes, platelets, clotting time, prothrombin time, total and differential leukocytes, erythrocyte morphology. Clinical chemistry: serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, alkaline phosphatase, bliid urea nitrogen, fasting glucose, total protein, albumin, globulin, A/G ratio, cholesterol, triglycerides, sodium, potassium, chloride, calcium, creatinine, lactic acid dehydrogenase, total bilirubin, direct bilirubin. Urinalysis: gross appearance, specific gravity, pH, protein, glucose, ketones, bilirubin, occult blood, microscopic analysis

Organs examined at necropsy: Organs weighed and organ/body weight ratios calculated: adrenals, brain, ovaries, testes (without epididymides), heart, kidneys, liver (with gall bladder attached), pituitary, spleen, thyroid (with parathyroid). Tissues examined histopathologically: adrenal, aorta (thoracic, arch, lumbar), bone and bone marrow (sternum), brain, epididymus, esophagus, eye, heart, intestine, cecum, colon, rectum, kidney, liver with gall bladder, lungs with mainstem bronchi, lymph nodes (cervical, peribronchial, mesenteric), nerve (left sciatic), oral mucous membrane (including tongue, buccal, maxillary gingiva, pharynx and nasopharynx), ovary, pancreas, pituitary, prostate, salivary gland (submaxillary), skeletal muscle (biceps femoris), skin with mammary gland (left inguinal), spinal cord (cervical, thoracic, lumbar), spleen, stomach (cardia, pylorus, fundus), testis, thymus, thyroid with parathyroid, trachea, urinary bladder, uterus (corpus, cervix, fallopian tubes), vagina, gross lesions, tissue masses or suspect tumors and regional lymph nodes.

Reliability : (2) valid with restrictions
Well conducted study, prior to GLP

05.12.2003 (2)

Type	:	
Species	:	rat
Sex	:	male/female
Strain	:	Wistar
Route of admin.	:	oral feed
Exposure period	:	24 months
Frequency of treatm.	:	daily
Post exposure period	:	none
Doses	:	100, 500 ppm
Control group	:	yes, concurrent no treatment
NOAEL	:	500 ppm
Method	:	other: NIHMR method
Year	:	1983
GLP	:	no
Test substance	:	Chemical name: 2,4,8,10-tetraoxa-3,9-diphosphaspiro [5.5]undecane, 3,9-bis[2,4-bis(1,1-dimethylethyl)phenoxy]- CAS No.: 26741-53-7 Trade name: Weston XP1452 Purity: 99%

Result : Body weight: No diference was observed between the average weights of the control group and treated animals.

Food/water consumption: No difference was observed between the treated groups and the control group animals.

Clinical signs: No difference between the treated animals and the control group. Toward the 18th month, the animals began to show signs of ageing, i.e. some of them had a yellow coat, dyspnoea, pulmonary insufficiency and dark rings around the eyes, but these symptoms were relatively rare and no more frequent among the treated animals than among the control animals.

Hematologic findings: The haemoglobin level, the haematocrit, the number of erythrocytes and the level or relative number of leucocytes were the same in all the groups.

Clinical biochemistry: No difference in glucose levels, ureic nitrogen levels, the GOT, the GPT, the PA, total proteins and the albumin levels were seen.

Renal function: The urine density showed no significant variation and neither did the proteinurea, glycosuria and urinary residue examinations.

Mortality:

Dose (mg/kg)	Sex	Total Deaths	Months to death (No. of animals)
0	Male	11	13(1), 19(4), 20(1), 21(3), 22(2)
	Female	5	20(1), 21(2), 22(2)
100	Male	9	12(1), 13(1), 15(1), 16(1), 17(1), 20(1). 21(2), 22(1)
	Female	5	19(1), 21(3), 22(1)
500	Male	15	13(1), 14(2), 15(1), 16(1), 17(3), 18(1), 20(1), 21(1), 22(4)
	Female	6	14(2), 15(1), 21(1), 23(1)

Mortality was higher among the males than among the females. A dose of 100 ppm did not give rise to higher mortality amog the male or female rats compared to the control group. At 500 ppm, mortality is no higher among the female rats, but higher mortality was observed among the male rats. The authors concluded that this difference was not significant.

Gross pathology: an examination of the main organs did ot reveal any significant difference between the treated rats and the control group. The animals often showed clear organic pathological signs of aged animals which could in no case be attributed to the treatment since they appeared with equal frequency in the control group.

Organ weight changes: No change in the weight of the main organs under the effect of the treatment was seen.

Histopathology: No greater frequency of anomalies in the organs of the treated rats compared with the control group.

Test condition : Test subjects

Age at study initiation: no data

Study Design

Vehicle: Feed

Clinical observations: Each animal was weighed every week over the first four weeks, twice a week during weeks 6-12 and then every other week after week 12. Food and water intake was measured in weeks 1+3, 3+4, 11+12, 23+24, 38+39, 52+53, 75+76, 86+87 and 97+98.

Haematological examinations were conducted during weeks 12, 24, 52, 88 and 104. The blood was used:

a) to conduct measurement of haemoglobin content, haematocrits, number of erythrocytes and leucocytes and leucocytic formula;
b) to determine blood glucose and ureic nitrogen levels;
c) to analyze for the following enzymatic activities: glutamic-pyruvate transaminase, alkaline phosphatase and proteins and albumin serum.

Urine was collected in weeks 12, 24, 53, 98-104 and tested for appearance, pH, glucose, proteins, density, blood, lymphocytes and erythrocytes, epithelial cells, urate and phosphate crystals and evaluation of the bacterial population.

Organs examined at necropsy: The main oragans were subjected to a macroscopic examination and some were weighed (liver, kidneys, splen, brain, heart, supra-renal bodies and hypophysis). Tissue fragments were taken: heart, kidney, liver, pancreas, spleen, brain, ovary or testicle, thyroid, suprrenal bodies, thymus, lung, trachea, salivary glands, stomach, duodenum, colon, caecum and uterus.

Reliability : (2) valid with restrictions
10.12.2003 (5)

i.p **GENETIC TOXICITY 'IN VITRO'**

Type	:	Ames test
System of testing	:	Salmonella typhimurium strains TA97, TA 98, TA100, TA102 Escherichia coli Strain WP2 (PKM101)
Test concentration	:	50 – 2000 µg/Plate
Cycotoxic concentr.	:	
Metabolic activation	:	with and without
Result	:	negative
Method	:	other: Hachiya (1994)
Year	:	1994
GLP	:	no data
Test substance	:	Chemical name: 2,4,8,10-tetraoxa-3,9-diphosphaspiro [5.5]undecane, 3,9-bis[2,4-bis(1,1-dimethylethyl)phenoxy]- CAS No.: 26741-53-7
Test condition	:	Solvent: Acetone and Tween 80
Reliability	:	(4) not assignable Secondary literature data

08.12.2003 (8)

Type	:	Chromosomal aberration test
System of testing	:	Chinese hamster ovary cells
Test concentration	:	31.3-2000 µg/mL (-S9, 4 hour exposure), 31.3 – 3000 µg/mL (+S9, 4 hour exposure; -S9, 20 hour exposure)
Cycotoxic concentr.	:	500 µg/mL (+S9), 2000 µg/mL (-S9)

Result	:	positive
Method	:	OECD Guide-line 473
Year	:	2003
GLP	:	yes
Test substance	:	Chemical name: 2,4,8,10-tetraoxa-3,9-diphosphaspiro [5.5]undecane, 3,9-bis[2,4-bis(1,1-dimethylethyl)phenoxy]- CAS No.: 26741-53-7 Trade name: Ultranox 626 Lot No.: H42265
Method	:	METHOD Metabolic activation: Arochlor 1254-induced rat liver S(9) Concentrations tested: Experiment 1: 31.3, 62.5, 125, 250, 500, 1000 µg/mL (-S9, 4 hour exposure) 31.3, 62.5, 125, 250, 500, 1000, 1500, 3000 µg/mL (-S9, 20 hour exposure) 31.3, 62.5, 125, 250, 500, 1000, 1500, 3000 (+S9, 4 hour exposure) Statistical Methods: Statistical analysis of the percent aberrant cells was performed using Fisher's exact test. Fisher's exact test was used to compare pairwise the percent aberrant cells of each treatment group with that of the solvent control. In the event of a positive Fisher's exact test at any test article dose level, the Cochran-Armitage test was used to measure dose-responsiveness.
Result	:	+S9, 4h exposure: The percentage of cells with structural aberrations in the test article treated group was statistically increased above that of the solvent control at 250 µg/mL (p=0.05, Fisher's exact test). The Cochran-Armitage test was also positive for a dose response (p<0.05). However, the percentage of cells with structural aberrations in the test article treatd group (6.0%) was within the historical solvent control range of 0.0 – 6.5%. Therefore it is not considered to be biologically significant. The percentage of cells with numerical aberrations in the test article treated groups was not significantly increased above that of the solvent control at any dose level (p>0.05, Fisher's exact test). –S9, 20h exposure: The percentage of cells with structural or numerical aberrations in the test article treated groups was not significantly increased above that of the solvent control at any dose level (p>0.05, Fisher's exact test). –S9, 4h exposure: Due to the lack of dose levels with =5-% toxicity relative to solvent control in this group, the experiment was repeated at higher dose levels. –S9, 4h exposure (repeat): The percentage of cells with structural aberrations in the test article treated groups was significantly increased above that of the solvent control at 2000 µg/mL (p=0.05, Fisher's exact test). The Cochran-Armitage test was also positive for a dose related response (p<0.05). The percentage of cells with numerical aberrations in the test article-treated groups was not significantly increased above that of the solvent control at any dose level (p=0.05, Fisher's exact test).
Test condition	:	Test Design Number of replicates: Duplicate tests Positive and negative controls and treatment: Mitomycin C was used as the positive control in the non-activated study at final concentrations of 0.1 and

activated study at final concentrations of 10 and 20 µg/mL. The solvent for the test article (DMSO) was used as the solvent control at the same concentration as that found in the test article-treated groups.

Solvent: dimethylsulfoxide

Number of metaphases analyzed: Whenever possble, a minimum of 200 metaphase spreads (100 per duplicate flask) were examined and scored for chromatid-type and chromosome-type aberrations. The number of metaphase spreads that were examined and scored per duplicate flask was reduced when the percentage of aberrant cells reached a statistically significant level before 100 breaks were scored.

Description of follow up repeat study: Due to lack of dose levels with 50% toxicity relative to the solvent control in the non-activated 4 hour exposure group, the chromosome aberration assay was repeated in that group at dose levels of 250, 500, 1000, 1250, 1500 and 2000 µg/mL.

Criteria for evaluating results: The test article was considered to induce a positive response when the percentage of cells with aberrations increased in a dose-responsive manner with one or more concentrations being statistically significant (p=0..5). However, values that were statistically significant but did not exceed the range of historic solvent controls was judged as not biologically significant. Test articles not demonstrating a statistically significant increase in aberrations were concluded to be negative.

Conclusion : Under the conditions of the assay described in this study, the test material was concluded to be weakly positive for the induction of structural and negative for the induction of numerical chromosome aberrations in CHO cells in the absence of metabolic activation. The test material was concluded to be negative for the induction of structural and numerical chromosome aberrations in CHO cells in the presence of metabolic activation.

Reliability : (1) valid without restriction
25.11.2003 (7)

i.p **GENETIC TOXICITY 'IN VIVO'**

Type	:	Micronucleus assay
Species	:	mouse
Sex	:	male/female
Strain	:	ICR
Route of admin.	:	i.p.
Exposure period	:	24, 48 hours
Doses	:	500, 1000, 2000 mg/kg
Result	:	negative
Method	:	OECD Guide-line 474 „Genetic Toxicology: Micronucleus Test"
Year	:	2003
GLP	:	yes
Test substance	:	Chemical name: 2,4,8,10-tetraoxa-3,9-diphosphaspiro [5.5]undecane, 3,9-bis[2,4-bis(1,1-dimethylethyl)phenoxy]- CAS No.: 26741-53-7 Trade name: Ultranox 626 Lot No.: H42265

Result : Effect on mitotic index or PCE/NCE ratio by dose level by sex: See table below

Genotoxic effects: Negative

Mortality at each dose level by sex:

Pilot toxicity study: No mortality occurred at any doses during the course of the study.

Main study: No mortality occurred at any dose during the course of the micronucleus study.

Clinical signs:

Pilot toxicity study: All animals appeared normal except male mice at 2000 mg/kg, which exhibited piloerection.

Main study: Piloerection was seen in all male and female mice at 1000 and 2000 mg/kg. All other mice appeared normal during the study.

Bodyweight changes:

Pilot toxicity study: Change in group mean bodyweights ranged from –0.3% (1.0 mg/kg) to 4.5% (1000 mg/kg) after 3 days.

Mutant/aberration/mPCE/polyploidy frequency, as appropriate: See table below.

Food/water consumption: no data

Test condition : Age at study initiation: 6 – 8 weeks old at the initiation of each phase of the study.

No. of animals per dose:
Pilot toxicity study: 2 male mice dosed at 1, 10, 100 or 1000 mg/kg b.w.; 5 male and 5 female mice dosed at 2000 mg/kg.

Main study: Groups of 5 male/5 female mice dosed at 0, 500, 1000, 2000 mg/kg (euthanized at 24 h); Groups of 5 male/5 female dosed at 0, 2000 mg/kg (euthanized at 48 h).

Route: i.p.

Vehicle: Corn oil.

Controls: Vehicle (Corn oil), cyclophosphamide monohydrate (positive).

Clinical observations performed: Clinical signs, mortality, bodyweight

Organs examined at necropsy: none

Criteria for evaluating results: The incidence of micronucleated polychromatic erythrocytes per 2000 polychromatic erythrocytes was determined for each mouse and treatment group. Statistical significance was determined using the Kastenbaum-Bowman tables which are based on the binomial distribution. In order to quantify the proliferation state of the bone marrow as an indicator of bone marrow toxicity, the proportion of polychromatic erythrocytes to total erythrocytes was determined for each animal and treatment group. The test article was considered to induce a positive response if a dose-responsive increase in micronucleated polychromatic erythrocytes was observed and one or more doses were statistically elevated relative to the vehicle control ($p<=0.05$, Kastenbaum-Bowman Tables) at any sampling time. However, values that were statistically significant but did not exceed the range of historical negative or vehicle controls were judged as not biologically significant. The test article

no evidence of dose responses were observed at any sampling time.

Criteria for selection of M.T.D.: based on preliminary toxicity study.

Table: Summary of Bone Marrow Micronucleus analysis

Treatment (20mL/kg)	Sex	Time (hr)	No. of mice	PCE/Total Erythrocytes (mean ± SD)	Change from Control (%)	Micronucleated Polychromatic Erythrocytes	
						Number per 1000 PCEs (mean ± SD)	Number per PCEs Scored[1]
Corn oil	M	24	5	0.456±0.07	-	0.6±0.22	6/ 10000
	F	24	5	0.526±0.09	-	0.5±0.35	5/ 10000
Test article							
500 mg/kg	M	24	5	0.477±0.06	5	0.6±0.22	6/ 10000
	F	24	5	0.462±0.04	-12	0.6±0.42	6/ 10000
1000 mg/kg	M	24	5	0.480±0.06	5	0.7±0.27	7/ 10000
	F	24	5	0.543±0.05	3	0.8±0.27	8/ 10000
2000 mg/kg	M	24	5	0.493±0.09	8	0.5±0.00	5/ 10000
	F	24	5	0.469±0.04	-11	0.3±0.27	3/ 10000
CP[2]	M	24	5	0.335±0.03	-27	22.2±2.20	*222/ 10000
50 mg/kg	F	24	5	0.325±0.01	-38	20.4±2.43	*204/ 10000
Corn oil	M	48	5	0.502±0.06	-	0.3±0.27	3/ 10000
	F	48	5	0.483±0.05	-	0.6±0.22	6/ 10000
Test article							
2000 mg/kg	M	48	5	0.447±0.05	-11	0.6±0.22	6/ 10000
	F	48	5	0.495±0.05	2	0.5±0.35	5/ 10000

[1]*statistically significant, p<=0.05 (Kastenbaum-Bowman Tables).
[2] cyclophosphamide monohydrate

Reliability : (1) valid without restriction
26.11.2003 (6)

5.8.1 TOXICITY TO FERTILITY

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species : rabbit
Sex : female
Strain :
Route of admin. : oral unspecified
Exposure period : Days 6 to 18 of gestation
Frequency of treatm. : daily
Duration of test : Fetuses removed on day 29 of gestation
Doses : 0, 20, 50, 200 mg/kg
Control group : yes
Method : other: NIHMR method
Year :
GLP :
Test substance : Chemical name: 2,4,8,10-tetraoxa-3,9-diphosphaspiro [5.5]undecane, 3,9-bis[2,4-bis(1,1-dimethylethyl)phenoxy]-
CAS No.: 26741-53-7
Trade name: XP1452

Result : No maternal effects (i.e. body weights, clinical and pathological observations) were noted in any dose group.

3/15 rabbits miscarried in the high dose group (200 mg/kg) however, this finding was considered only bordering significance.

were not significantly diferent from the control values.

There was no difference in the distribution between male and female fetuses and there was not a significant number of malformations observed (1 fetus with aplasia of the head at 50 mg/kg and 1 fetus with internal hydrocephalus at 200 mg/kg).

Conclusion : The authors did not consider the substance to be a teratogenic agent.
Reliability : (4) not assignable
12.12.2003

(12)

(1) Ben-dyke, R (1980), Biodynamics, Acute toxicity study in the chicken on Weston 1532, Project No. 6234-80

(2) Bio/dynamics Inc. (1980), A four month oral toxicity study with Weston XR 1532 in dogs, Project No. 79-2411

(3) Bio/dynamics Inc. (1981) Primary Dermal Irritation Study in Rabbits, Project No. 6772-81

(4) Brett, B (1975) Industrial Bio-Test Laboratories, Acute oral toxicity study with CDP-1106 in albino rats, Report No. 601-07166; in, unpublished Toxicity Summary of Ultranox 626, prepared by GE Specialty Chemicals, 1997

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